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EFFICACY OF BOTOX INJECTION AROUND SCALP NERVES AS PROPHYLAXIS FOR CHRONIC DAILY HEADACHE

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ABSTRACT

Objective

To assess the efficacy and safety of low doses of botulinum toxin type A (BoNT-A) for the prophylaxis of headaches in patients with chronic daily headache (CDH) in a new mapping of infiltration.

Design and Methods

This was a prospective -controlled 6 months study for 112 patients with CDH. Compared between two groups of patients, Group I - 65 patients treated with medication (classic method) and Group II - 47 patients treated by BoNTA. Patients monthly recorded for day occurrence, frequency, severity and associated headache symptoms.

Results

All time points of the 6-month study, there was a statistical significant decrease in the mean change from baseline for the frequency, number and severity of headaches for BoNT-A group as compared with classical one. In the classical group frequency decreased from 11.57 to 8.94 (22 % reduction) while in BoNT-A the frequency decreased from 12.19 to 3.85 (68 % reduction) p= .001. Regarding mean number of headaches per month, classical group from 21.25 to 11.23 (47% reduction); BoNT-A: from 22.11 to 5.91 (73 % reduction); P = .001. Mean headache severity in the BoNT-A group: no pain 24 (51.1%), mild 22 (46.8%), moderate 1 (2.1%) and no one severe pain as compare with classical method no pain 22 (33.8%), mild 29 (44.6%), moderate 13 (20.0%) and one case severe pain (1.5%) P= 021. Except for sensitivity to light, sound other associated symptom nausea, vomiting and headache with physical activity there was statistical significant decrease in the BoNT-A as compared to classical group P=.042, .032 and .021 respectively.

Conclusions

The small doses of the BoNT-A without using other prophylactic medications is an effective and well-tolerated prophylactic treatment in patients with CDH.

KEYWORDS: Headache, Chronic Daily Headache, Bont-A and Classical Group and BOTOX

INTRODUCTION

The term chronic daily headache (CDH) begins as episodic migraine or tension-type headache and progresses to chronic daily headache, especially in association with medication overuse. It is occurring on more than 15 days a month for more than 3 months and lasting for more than 4 hours per day if untreated. 1-4 in adults, 4-5% of the general population have CDH. 5

The management of patients with CDH represents one of the major challenges for practicing clinicians. The use of

prophylactic medications for CDH is supported mainly by open-label studies. A few controlled studies have been performed; however, these studies do not account for symptomatic medication overuse or concomitant prophylactic medication as major confounders, or do not provide specific diagnoses for patients with CDH. 6-7

BoNT-A has been used in several neurological diseases such as dystonia, spasticity, hyperhydrosis and sialorrhea8-9. In cervical dystonia, pain is relieved more satisfactorily than torticollis, and tipically it is perceived before muscle relaxation is observed6.10

Mechanism of Action

BOTOX blocks neuromuscular transmission by binding to acceptor sites on motor or sympathetic nerve terminals, entering the nerve terminals, and inhibiting the release of acetylcholine. This inhibition occurs as the neurotoxin cleaves SNAP-25, a protein integral to the successful docking and release of acetylcholine from vesicles situated within nerve endings. When injected intramuscularly at therapeutic doses, BOTOX produces partial chemical denervation of the muscle resulting in a localized reduction in muscle activity. In addition, the muscle may atrophy, axonal sprouting may occur, and extrajunctional acetylcholine receptors may develop. There is evidence that reinnervation of the muscle may occur, thus slowly reversing muscle denervation produced by BOTOX.11-14

In preclinical studies, BoNTA has also been shown to block the release of nociceptive mediators such as substance P, glutamate, and calcitonin gene-related peptide (CGRP) at non-cholinergic, non-motor neurons via SNAP-25 cleavage (11–14). Cui and colleagues have demonstrated that local peripheral injection of BoNTA significantly reduces formalin-induced nociceptive behaviour in rats in a dose-related manner with an absence of obvious muscle weakness (13). A small, open-label preliminary study of the analgesic effects of BoNTA in humans found that while BoNTA did inhibit peripheral neuropeptide release from nociceptive nerve fibers, its analgesic effects were reported by the authors to be limited (15). These results may have been influenced by the model used in this study since an electrical stimulus was applied directly to stimulate the pain nerve. The BoNTA pretreatment was only able to inhibit the peripheral nociceptive peptide release (measured as neurogenic flare) in the volunteers. Since BoNTA does not cross the blood–brain barrier and is not transported centrally by the nerve, there was no effect of BoNTA on hyperalgesia or allodynia elicited by electrical stimulation. In the preclinical studies, BoNTA was effective in situations where sufficient peripheral sensitization (i.e. formalin or capsaicin) could be achieved, so BoNTA may inhibit the peripheral release of nociceptive signals and thus reduce sensory input into the central nervous system (CNS) (12). Further clinical studies of this effect in humans are needed to confirm the results of preclinical studies. 16-18

METHODS

Study Design

This prospective -controlled 6 month study for 112 patients with CDH was conducted from Jan 2011 to Jan 2014. All patients had a diagnosis of CDH according to International Headache Society (IHS) criteria. The mean age was 34 years old, mean age of onset 22.77 years, mean duration of headache 11.23 years, 79 females 33 males. At baseline, some patients reported associated symptoms with their headaches. These symptoms included sensitivity to light or sound [42 (37.5%)], nausea [37 (33.0%)] and vomiting [21 (18.8%)]. Pain associated with daily activity or menstrual period in female [60 (53.6%)].

The change from baseline in headache severity based on scale from 0 to 3 corresponding from none to severe

[0 = none, 1 = mild, 2 = moderate, 3 = severe] per 30-day periods.14, 17

Pain score for the participant were mild 32 (28.6%), moderate 58 (51.8%) and severe 22 (19.6%).

The Patients With CDH Were Assigned Into Two Groups:

Group I- 65 patients treated with medication (classic method): this involved withdrawing medicine in patients with medication overuse. Then analgesic with symptomatic treatment was given. Amitriptyline and sodium valproate were added if no response.

Group II- 47 patients treated by BoNTA: They were prevented from takes the analgesics that were currently used before the beginning of the study. No patient used analgesics containing narcotics. The most commonly used on need paracetamol with or without caffeine.

There was no statistically significant difference between group 1 and 2 concerning age, sex, headache frequency, analgesic intake, headache diagnosis, and questionnaires ranks of anxiety, depression and life quality.

This study was conducted in compliance with the ethical principles in the Declaration of Helsinki regarding biomedical research on human subjects and with standard informed consent regulations. Prior to study initiation, the investigators obtained Institutional Review Board's approval.

Efficacy Measures

Post-injection follow-up evaluations were scheduled on days 30, 60, 90, 120, 150 and 180.

At each study visit, participants were given a month paper diary and instructed to complete it on a daily basis throughout the study. Patients recorded the day occurrence, frequency, severity; associated headache symptoms (nausea, vomiting, increased sensitivity to light and/or noise, and worsening head pain with physical activity); percentage of each day with headache, as calculated from the hours awake with headache as a proportion of those hours; headache medications with dose and time of dose.

Safety Measures

All patients had a normal neurological examination, investigations, brain CT scan and were instructed to fill out questionnaires of self-evaluation for depression, anxiety and life quality.

Environmental factors were not controlled during the study period, but no specific advices were given concerning daily activities, sleep or food habits, to the patients or their families.

Each vial of BOTOX ® (Allergan, Inc.) was stored in a freezer between −20°C and −5°C before use and contained 100 U of botulinum toxin type A, 0.5 mg albumin (human) and 0.9 mg sodium chloride in a sterile, vacuum-dried form without a preservative. BOTOX was reconstituted with 10 ml of the diluent, 0.9% sterile saline (without preservative).

In this study doses of BoNT-A injection mention in the table 1 infiltrated around main nerve of the scalp supraorbital, temporal, greater and lesser occipital nerve at the point entrances to the scalp.

Table 1: Bont-A Dosing Injection Main Nerve of the Scalp for CDH

Nerve Scalp Supply	Botox Dose (Dose Distributed Bilateral)
Supraorbital nerve	5 Unite
Superficial temporal nerve	20 Unite
Greater occipital nerve	20 Unite
Lesser occipital nerve	20 Unite
Total Dose	**65 Unite**

Statistical Analyses

The following tests were used for statistical analysis:

- Student t-test was used to compare the difference in the means of number of days of headache attacks and frequency of headache attacks in the classical and BoNT-A group.
- Chi-squared or Fisher Exact's tests was used to compare the differences in the pain score, sensitivity to light, sound, nausea, vomiting and headache with physical activity in the classical and BoNT-A group.

RESULTS

Demographics and Baseline Characteristics

Group I included 65 patients (45 female, 20 male) and group II, 47 patients (34 female, 13 male).

Efficacy

Frequency of Headaches: We observed that both groups had a significant decrease of headache frequency when we compared the initial baseline frequency with that recorded at the end of the sex months of the study period.

In the six months period the mean monthly headache frequency decreased from 11.57 to 8.94 (22 % reduction), in group I, while in group II, the frequency decreased from 12.19 to 3.85 (68 % reduction) p= .001

Number of Headaches: The baseline mean number of headaches per month was no statistical differences' for the two groups before treatment (classical: 21.25 headaches; BoNT-A: 22.11; P = .073).

Beginning within the first month of treatment, and throughout the treatment phase of the 6-month study, there was a decrease in the mean change from baseline for the number of headaches in both treatment groups. At all time points, the mean decrease from baseline was statistical significant greater decrease in the BoNT-A group (classical: 11.23 (47% reduction); BoNT-A: 5.91 (73 % reduction); P = .001).

Headache-Free Days: During the course of treatment the mean change in headache free days for classical group 10 while in BoNT-A group 16. Beginning with the first month of treatment, the mean change from baseline in the number of headache-free days improved over the course of the study in both treatment groups but the increase was greater in the BoNT-A group than the classical group.

Table 2: Number and Frequency of Headache Before and after Treatment

		Group	Mean	Std. Deviation	P Value
Base line	Number of headache	Classical method	21.25	2.592	.073
		Botox Injection	22.11	2.220	
	Frequency of headache	Classical method	11.57	1.763	.081
		Botox Injection	12.19	1.442	
During period of study	Number of headache	Classical method	11.23	2.656	.001
		Botox Injection	5.91	1.898	
	Frequency of headache	Classical method	8.94	2.364	.001
		Botox Injection	3.85	1.103	

Headache Severity: At baseline, degree of headache severity was similar for the two treatment groups. Mean usual headache severity statistically significant decreased over the course of the study in both groups but was more decrease in the BoNT-A group no pain 24 (51.1%), mild 22 (46.8%), moderate 1 (2.1%) and no one severe pain as compare with classical method no pain 22 (33.8%), mild 29 (44.6%), moderate 13 (20.0%) and one case severe pain (1.5%) P= 021.

Associated Symptoms: During the 120-day baseline period of the study, was significantly reduced in associated symptoms in both groups. In classical group sensitive to light, sound and nausea 13 (20.0%), vomiting 9 (13.8%), associated activity 24(36.9%) while in BoNT-A group sensitive to light, sound 5 (10.6%), nausea 3(6.4%), vomiting 1 (2.1%), associated activity 8(17.0%). Although there was a reduction in sensitive to light, sound more BoNT-A-treated patients compared with classical but it is not statistically significant P=.183 while it is statistically significant for nausea, vomiting and associated activity P=.042, .032 and .021 accordingly.

Table 3: Compared Results of Headache Severity and Associated Symptoms

		Group		Pearson Chi-Square
		Classical Method	Botox Injection	
Pain score	No pain	22	24	.021
		33.8%	51.1%	
	mild	29	22	
		44.6%	46.8%	
	moderate	13	1	
		20.0%	2.1%	
	severe	1	0	
		1.5%	0.0%	
sensitive to light, sound after R		13	5	.183
		20.0%	10.6%	
nausea after R		13	3	.042
		20.0%	6.4%	
vomiting after R		9	1	.032
		13.8%	2.1%	
associated activity after R		24	8	.021
		36.9%	17.0%	

Safety and Tolerability: During the course of the study, there was 7 cases from classical group developed gastric intolerance to medication 4 cases shifting to BoNT-A group to avoid long use drug with rapid onset pain relive. 2 cases in BoNT-A group had blepharoptosis less than 2 weak. More study and cases required to compare adverse effect of both methods.

DISCUSSIONS

Considering the whole study period (six months), our study showed a statistically significant decrease in headache number, frequency and severity.

Although several patients exhibited psychological traits suggestive of depression and anxiety, we could not establish their role in headache frequency variation due to the small sample size.

The low number of patients that completed the study could be a confounding factor in the interpretation of the results. A high dropout rate with studies using this methodology and the long treatment period is a problem frequently observed. We agree that a higher number of patients would be desirable.

However, for all efficacy parameters there was a greater effect for BoNT-A compared with classical, and at many time points statistically significant differences favoring BoNT-A treatment were observed. This was particularly the case for the frequency of headaches per 30-day periods. BoNT-A treatment also showed greater improvement in the number of headache-free days.

There are a study changes in the curve of mean frequency and change free days in BoNT-A group as compared with classical group as show in figure 1 and 2. This might be due to drug more stable in BoNT-A group rather than classical group.

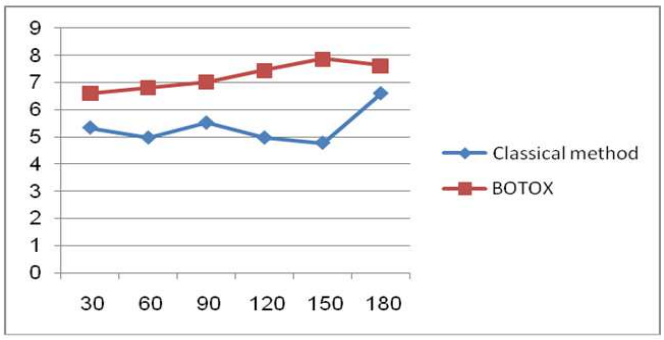

Figure 1: Compare of Mean Frequency of Classical with Bont-A Group

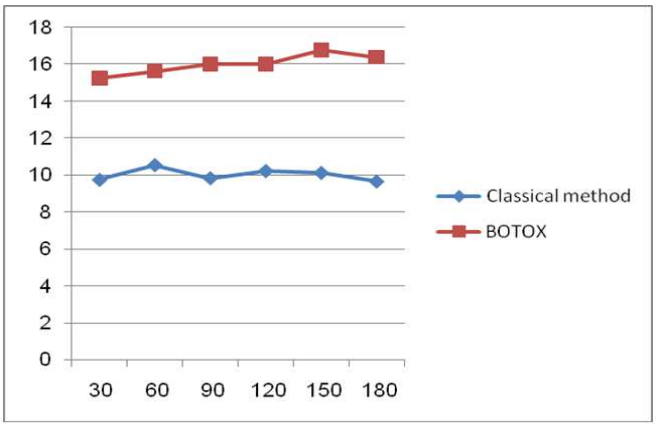

Figure 2: Compare of Mean Change Free Days from Pain of Classical with Bont-A Group

Some Studies Effect Bont-A on Headache

Sixty patients with headaches of more than 15 days per month were recruited for this double-blind,

placebo-controlled, parallel study of botulinum toxin type A (BTX) for chronic tension type and chronic migraine headaches. the number of headache-free days as assessed by diary for 12 and 24 weeks after BTX injection. They received either 200 U of BTX or matching placebo and were followed. Similarly 200 U of BTX followed for another 12 weeks. Over a 12-week period after injections, headache-free days had improved in the BTX group from week 8 to 12 ($P < 0.05$), but did not meet the *a priori* significance criteria over the entire 12-week period, 33 ± 23 vs. 24 ± 16 days without headache ($P = 0.07$). At week 24 (open label), headache-free days were less in the twice BTX injected group compared with the once injected group, 40 ± 26 vs. 26 ± 19 ($P < 0.05$).20

BOTOX was evaluated in two randomized, multi-center, 24-week, 2 injection cycle 155 units divided in 31 sites, placebo-controlled double-blind studies. Study 1 and Study 2 included chronic migraine adults who were not using any concurrent headache prophylaxis, and during a 28-day baseline period had >15 headache days lasting 4 hours or more, with >50% being migraine/probable migraine. In both studies, patients were randomized to receive placebo or 155 Units to 195 Units BOTOX injections every 12 weeks for the 2-cycle, double-blind phase. Patients were allowed to use acute headache treatments during the study. BOTOX treatment demonstrated statistically significant and clinically meaningful improvements from baseline compared to placebo for key efficacy variables

Table 4

Efficacy per 28 days	Study 1		Study 2	
	BOTOX (N=341)	Placebo (N=338)	BOTOX (N=347)	Placebo (N=358)
Change from baseline in frequency of headache days	-7.8*	-6.4	-9.2*	-6.9
Change from baseline in total cumulative hours of headache on headache days	-107*	-70	-134*	-95

* Significantly different from placebo ($p<0.05$)

Patients treated with BOTOX had a significantly greater mean decrease from baseline in the frequency of headache days at most time points from Week 4 to Week 24 in Study 1 and all time points from Week 4 to Week 24 in Study 2 compared to placebo-treated patients. 15-18

Three hundred patients studied the safety and efficacy of 0 U, 50 U, 100 U, 150 U (five sites), 86 Usub and 100 Usub (three sites) BoNT-A for the prophylaxis of chronic tension-type headache (CTTH). For the primary endpoint, the mean change from baseline in the number of TTH-free days per month, there was no statistically significant difference between placebo and four BoNTA groups, but a significant difference favouring placebo vs. BoNTA 150 was observed (4.5 vs. 2.8 tension headache-free days/month; P = 0.007). 21. The comparisons between of our results with above studies are complicated by differences in study design, sample size, patient populations (eg, severity of the disorder as reflected in baseline headache frequency and/or days of headache), and the choice of efficacy measures and assessment time points, the role of the BoNT-A injection (all studies of BoNT-A treatment of headache injected into multiple sites reach to 31 and /or used high dose of BoNT-A 150- 250 unite in one 1- 3 sessions . in our study there are used small dose of BoNT-A (65 unit) for 8 site one session with good result.

Suggestion of Pain Relive when Bont-A Injection

- Same effect on the muscle. partial chemical denervation of the nerve resulting in a localized reduction in nerve activity (nerve bloke)

- Botox relieve muscle spasm around the nerve that break cycle of pain - more spasm – nerve compression

Thus, the efficacy and safety profile of BoNT-A demonstrated in this analysis suggest that BoNT-A is an effective, well-tolerated prophylactic treatment in patients with CDH who are not using other prophylactic Headache treatments. Furthermore, the results also suggest that assessment of the frequency of headaches is a sensitive measure of efficacy in this patient population and that future studies to confirm these findings are needed. 21

Comment

All types of chronic daily headache may be temporarily relieved by painkillers or anti-migraine treatments, but in many cases this relief is only partial and the effect diminishes over time. These treatments are not appropriate because they will make the condition worse. Weaknesses of the available treatment methods include the chronic use of multiple drugs as prophylaxis management from one side. From other side BOTOX injection is painful (Because of local anesthetic with BOTOX injection increased side effect of BOTOX) and has side effect of BOTOX injection correlated with increase dose so, by reducing the number of BOTOX injections with reduction in the dose and change in the site of injection, effective management of CDH is expected. This makes the method used in this study more preferred of BOTOX injection or the use of medication in future. Further study required to show effect of the Botox on peripheral neuron and compare this methods with local infiltration of Botox to the scalp muscle.

CONCLUSIONS

The results of this clinical study suggest that:

- BoNTA is a safe, well-tolerated intervention in patients with CDH. No discontinuations due to adverse events occurred, nor were any treatment-related serious adverse events reported.
- The small doses of BoNTA65 U effective.
- Cost tolerance
- No case resistance in severe CHD

REFERENCES

1. Silberstein SD, Lipton RB. Chronic daily headache. Curr Opin Neurol. 2000; 13: 277-283.
2. Saper JR, Silberstein SD, Lake AE 3rd, Winters ME. Double-blind trial of fluoxetine: chronic daily headache and migraine. Headache. 1994; 34:497-502.
3. Silberstein SD, Lipton RB, Solomon S, Mathew NT. Classification of daily and near daily headaches: proposed revisions to the IHS classification. Headache 1994; 34: 1-7.
4. Evers S. Status on the use of botulism toxin for headache disorders. Curr Opin Neurol 2006; 19: 310–5.
5. Tfelt-Hansen P, Nielsen SL. Patients numbers needed in prophylacticmigraine trials. Neuroepidemiology 1987; 6: 214-219.
6. Esposito SB, Gherpelli JLD. Chronic daily headaches in children and adolescents: a study of clinical characteristics. Cephalalgia 2004; 24: 476-482.

7. Spira PJ, Beran RG. Gabapentin in the prophylaxis of chronic daily headache: a randomized, placebocontrolled study. Neurology. 2003; 61:1753-1759.
8. Ondo W, Vuong K, Derman H. Botulinum toxin A for chronic daily headache: a randomized, placebo-controlled, parallel design study. Cephalalgia. 2004; 24: 60-65.
9. Mathew N, Frishberg BM, Gawel M, et al. Botulinum toxin type A (BOTOX®) for the prophylactic treatment of chronic daily headache: a randomized, double-blind, placebo-controlled trial. Headache. 2005; 45: 293-307.
10. Ondo WG, Gollomp S, Galvez-Jimenez N. A pilot study of botulinum toxin A for headache in cervical dystonia. Headache 2005; 45: 1073-1077.
11. Krymchantowski AV, Silva MT, Barbosa JS, Alves LA. Amitriptylineversus amitriptyline combined with fluoxetine in the preventive treatmentof transformed migraine: a double-blind study. Headache 2002; 42: 510-514.
12. International Headache Society. Guidelines for controlled trials of drugs in migraine and tension-type headache. Member's Handbook. Stockholm: Scandinavian University Press, 1998:109-159.
13. Stephen D. Silberstein. Botulinum toxin type A in the prophylactictreatment of chronic tension-type headache: A multicentre, double-blind, randomized, placebocontrolled, parallel-group study, Jefferson Digital Commons, July 2006.
14. Dolly O. Synaptic transmission: inhibition of neurotransmitterrelease by botulinum toxins. Headache.2003; 43(suppl 1):S16-S24.
15. F o n t e s - R i b e i ro CA. I-5-hydroxytryptophan in the prophylaxis of chronic tension-type headache: a double-blind randomized placebo-controlled study. Cephalalgia 1999; 19: 453.
16. Aoki KR. Evidence for antinociceptive activity of botulinum toxin type a in pain management. Headache. 2003; 43 (suppl 1):9-15.
17. Barrientos N, Chana P. Botulinum toxin type A in prophylactic treatment of migraine headaches: a preliminary study. J Headache Pain. 2003; 4: 146-151.
18. DavidW. Dodick, MD; Alexander Mauskop, MD, FAAN. Botulinum Toxin Type A for the Prophylaxis of Chronic Daily Headache: Subgroup Analysis of Patients Not Receiving Other Prophylactic Medications: A Randomized Double-Blind, Placebo-Controlled Study, December 14, 2004.
19. Gladstein J, Holden EW, Winner P, Linder S. Chronic daily headachein children and adolescents: current status and recommendations for the future. Headache 1997; 37: 626-629.
20. SD Silberstein, H Göbel, R Jensen, AH Elkind, R DeGryse, JMCM Walcott & C Turkel. Botulinum toxin type A in the prophylactic treatment of chronic tension-type headache: A multicentre, double-blind, randomized, placebocontrolled, parallel-group study, July 2006.